Phase I/II studies in HIV-infected patients receiving cART have shown that administration of 3 weekly subcutaneous (s.c.) injections of Recombinant Human Interleukin-7 (r-hIL-7) is safe and increase number of both naïve and memory CD4 and CDT T cells. Here, we report the pooled data from two phase II trials evaluating the effect of repeated cycles of r-hIL-7 with the objective of restoring and maintaining CD4+ T cell count over 500 cells/µL.

**r-hIL-7 treatment**

- **Product:** CYT107 - Purified glycosylated 152 amino acid recombinant human Interleukin-7
- **Mode of Administration:** A cycle = 3 weekly subcutaneous injections of CYT107 at the dose of 20 µg/kg
- **Intervention:** Subjects received a first “induction” cycle and they were eligible to receive new “maintenance” cycles if the CD4+ T cell count falls below 500 Cells/µL, when monitored at quarterly visit (every 3 months)
- **Primary biological activity end-point:** Restoration and maintenance of CD4+ Tcells > 500 cells/µL

### INSPIRE 2

- **INSPIRE 2 Control arm**
  - 23 included HIV-1-infected patients under cART for at least 12 months
  - Ages: 22 (20-24) years
  - HIV RNA (copies/ml): 200-1000 cells/µL
  - 2 years of follow up with a maximum of 4 cycles within 21 months and 3 cycles within 12 months

- **INSPIRE 2 CYT107 arm**
  - 419 patients included
  - 82 randomized HIV-1-infected patients under cART for at least 24 months
  - Ages: 22 (19-25) years
  - HIV RNA (copies/ml): <200 cells/µL
  - 2 years of follow up with a maximum of 4 cycles within 21 months and 3 cycles within 12 months
  - Control arm: Subjects received r-hIL-7 only after 12 months of follow up if their CD4+ count still below 500 cells/µL

### INSPIRE 3

- **INSPIRE 3 Control arm**
  - Double arm clinical trial conducted in Italy, Switzerland and South Africa
  - 92 randomized HIV-1-infected patients under cART for at least 24 months
  - Ages: 22 (19-25) years
  - HIV RNA (copies/ml): <200 cells/µL
  - 2 years of follow up with a maximum of 4 cycles within 21 months and 3 cycles within 12 months

- **INSPIRE 3 CYT107 arm**
  - 307 patients included
  - 82 randomized HIV-1-infected patients under cART for at least 24 months
  - Ages: 22 (20-24) years
  - HIV RNA (copies/ml): <200 cells/µL
  - 2 years of follow up with a maximum of 4 cycles within 21 months and 3 cycles within 12 months

The median time above 500 cells/µL for patients with a follow up of at least 21 months (N=76) was 13.7 (8.4, 20.1). That is half of these patients spent more than 63 % of their follow up with more than 500 CD4+ T cells/µL.

### Patients characteristics

**INSPIRE 2**

- Number of patients included: 23
- Ages (years): 41 (37-46)
- Female (%): 43 (21.1)
- Genotype (Ccr5/Alexis): Cx/Ax (10.4) %
- Time since diagnosis (years): 8 (6, 10)
- Duration of ARV treatment (years): 6 (5, 7)
- CD4+ T cell count (cells/µL): 263 (191-320)
- CD8+ T cell count (cells/µL): 404 (340-497)
- CD4+ T cell count ratio: 0.64 (0.57, 0.70)
- ProViral HIVDNA log10/100 CD4+ cells/µL: 2.46 (2.16,3.20)

**INSPIRE 3**

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- Ages (years): 307 (20-40)
- Female (%): 43 (21.1)
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### CD4+ T cell dynamics

- **CD4+ T cell dynamics after first complete cycle**
  - N=95
  - Median and IQR of CD4+ T cell count without preferential increase of the proportion of T reg cells

- **CD4+ T cell dynamics after a first complete cycle and according to the number of CYT107 injections received**
  - N=49
  - Median and IQR of CD4+ T cell count without preferential increase of the proportion of T reg cells

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  - N=49
  - Median and IQR of CD4+ T cell count without preferential increase of the proportion of T reg cells

### Factors associated with dropping below 500 cells/µL

After adjustment for the baseline CD4+ T cell count, there was no significant difference of the effect of the maintenance cycles compared to the initial cycle whereas receiving incomplete cycles with only one injection increased the probability to fall below 500 CD4+ T cells/µL.

- **Time spent above 500 CD4+ cells/µL**
  - Median and IQR of CD4+ T cells within second cycle according to the presence of ADA after the first cycle

### Adverse events (AE) - Related Adverse Events (RAE)

From the total of RAES, most of them were grade ≤1 (77.6%), grade 2 (20.7%) and grade ≥3 ≥3 (5.5% patients presented an anaphylactic/allergic reaction, and symptoms were resolve with anti-histaminic and corticosteroid treatment. Ten (10) patients presented AE grade ≥3 hypophosphatemia, of which 3 possible RAE. An AST/ALT elevation of grade 3 was reported in 1 patient as a probable RAE.

### Conclusions

Repeated cycles of r-hIL-7 was safe and led to a substantial increase of the time spent above 500 cells/µL. The clinical benefit of such strategy needs to be evaluated in phase III clinical trial.